Reference:
1. Sachs R, Frank M Fishman SK: Overview of clinical experience with glipizide, in *Glipizide: A Worldwide Review.* Princeton, NJ, Excerpta Medica, 1984, pp 163-172.

GLUCOTROL® (glipizide) Tablets
Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes mellitus (NIDDM, type II) after an adequate trial of dietary therapy has proved unsatisfactory.

CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to the drug or with diabetic ketoacidosis, with or without coma, which should be treated with insulin.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes* 19, supp. 2:747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly or people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to a clinical situation. Certain drugs tend to produce hyperglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C: GLUCOTROL (glipizide) was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of GLUCOTROL. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. GLUCOTROL should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas: GLUCOTROL should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL (glipizide), dialysis is unlikely to be of benefit.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL; in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.

Maximum Dose: The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.

HOW SUPPLIED: GLUCOTROL is available as white, dye-free, scored diamond-shaped tablets imprinted as follows: 5 mg tablet—Pfizer 411 (NDC 5 mg 0049-4110-66) Bottles of 100; 10 mg tablet—Pfizer 412 (NDC 10 mg 0049-4120-66) Bottles of 100.

CAUTION: Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF NEUROSCIENCE—Volume 10, 1987—Edited by W. Maxwell Cowan, Washington University; Eric M. Shooter, Stanford University School of Medicine; Charles F. Stevens, Yale University School of Medicine, and Richard F. Thompson, Stanford University. Annual Reviews Inc, 4139 El Camino Way, PO Box 10139, Palo Alto, CA 94303-0897, 1987. 693 pages, $31.

THE ARTERIAL ANATOMY OF SKIN FLAPS—George C. Cormack, MA, MB, ChB, FRCS (Ed), formerly Department of Anatomy, University of Cambridge, and Fellow of Queens' College, Cambridge, and B. George H. Lamberty, MA, MB, BChir, FRCS, Consultant Plastic Surgeon, Addenbrooke's Hospital, Cambridge, and Associate Lecturer, University of Cambridge. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 442 pages, $195.

ATLAS OF U.S. CANCER MORTALITY AMONG WHITES: 1950-1980—Linda Williams Pickle, PhD, and Thomas J. Mason, PhD, Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland; Niel Howard, ORI, Inc, Washington, DC: Robert Hoover, MD, and Joseph F. Fraumeni, Jr, MD, Epidemiology and Biostatistics Program, Division of Cancer Etiology, National Cancer Institute, Bethesda, Maryland. US Department of Health and Human Services, National Institutes of Health, Bethesda, MD 20892, 1987. 184 pages, price not given.

BEDSIDE LOGIC IN DIAGNOSTIC GASTROENTEROLOGY—James Christensen, MD, Professor, Division of Gastroenterology-Hepatology, Department of Internal Medicine, University of Iowa College of Medicine, Iowa City. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 165 pages, $18 (paperback).

CARDIOVASCULAR DISEASE—Volume 1 in A Profile of Health and Disease in America—Wrynn Smith, PhD. Facts On File, 460 Park Ave South, New York, NY 10016, 1987. 121 pages, $35.

DEGOWIN & DEGOWIN'S BEDSIDE DIAGNOSTIC EXAMINATION—Fifth Edition—Revised by Richard L. DeGowin, MD, Professor of Internal Medicine, University of Iowa College of Medicine, Iowa City. Macmillan Publishing Company, 866 Third Ave, New York, NY 10022, 1987. 980 pages, $29.95.

ESTROGEN REPLACEMENT THERAPY—R. Don Gambrell, Jr, MD, Clinical Professor, Department of Obstetrics and Gynecology and Physiology and Endocrinology, Medical College of Georgia, Augusta. Creative Informatics Inc, PO Box 1607, Durant, OK 74702-1607, 1987. 128 pages, price not given (paperback).

EVALUATING ORTHOPEDIC DISABILITY—A COMMONSENSE APPROACH—Second Edition—T. Rothrock Miller, MD, St Joseph Hospital and Cardinal Hill Hospital, Lexington, Kentucky, and senior consultant orthopedic surgeon, Shriners Hospital for Crippled Children and Federal Correctional Institute. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205, 1987. 104 pages, $21.95 (paperback).

EVALUATING PREVENTIVE CARE—REPORT ON A WORKSHOP—Louise B. Russell, a senior fellow in the Brookings Economic Studies Program, Washington, DC. The Brookings Institution, 1775 Massachusetts Ave, NW, Washington, DC 20036, 1987. 101 pages; $22.95 (cloth), $8.95 (paperback).

THE EXERCISING ADULT—Second Edition—Edited by Robert C. Cantu, MD, Chief, Neurosurgical Service, and Director, Service of Sports Medicine, Emerson Hospital, Concord, Massachusetts. Macmillan Publishing Co, 866 Third Ave, New York, NY 10022, 1987. 285 pages, $29.95.

FLEXNER: 75 YEARS LATER—A CURRENT COMMENTARY ON MEDICAL EDUCATION—Edited by Charles Vevier, PhD, Professor, Department of Psychiatry, UMDNJ-New Jersey Medical School, Newark. University Press of America, 4720 Boston Way, Lanham, MD 20706, 1987. 114 pages, price not given.

FOREIGN TRAVEL & IMMUNIZATION GUIDE—12th Edition—Hans H. Neumann, MD, Director of Preventive Medicine, Department of Health, Yale University School of Medicine, New Haven, Connecticut. Medical Economics Books, Box C-779, Pratt Station, Brooklyn NY 11205-9066, 1987. 80 pages, $12.50 (paperback).

GERIATRIC MEDICINE ANNUAL 1987—Edited by Richard J. Ham, MD, Professor and Distinguished Chair in Geriatric Medicine and Director, Program in Geriatrics, State University of New York, Health Sciences Center at Syracuse, and President-Elect, American Geriatrics Society. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205. 278 pages, $35.95.

HANDBOOK OF GASTROINTESTINAL IMAGING—R. Kristina Gedgaudas-McClees, MD, Associate Professor, Department of Radiology, Emory University School of Medicine, Atlanta. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 257 pages, $49.

HEMATOLOGIC PROBLEMS IN PREGNANCY—Edited by David Z. Kitay, MD, Associate Professor of Obstetrics and Gynecology, University of South Alabama College of Medicine, Mobile. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205-9066, 1987. 408 pages, $39.95 (paperback).

KILL AS FEW PATIENTS AS POSSIBLE—Oscar London, MD, WBD. Ten Speed Press, PO Box 7123, Berkeley, CA 94707, 1987. 102 pages, $7.95 (paperback).

LIVING WITH MEDICINE: A FAMILY GUIDE—Edited by Mary Evelyn C. Smith. American Psychiatric Association Auxiliary, 1400 K St, NW, Washington, DC 20005, 1987. 262 pages, $17.95 (paperback).

MANUAL OF CATARACT SURGERY—Robert M. Sinskey, MD, Associate Clinical Professor of Ophthalmology, UCLA School of Medicine, Los Angeles, and Medical Director, Southern California Lions' Eye Institute, Santa Monica, and Jay V. Patel, MD, Clinical Instructor of Ophthalmology, UCLA School of Medicine, Los Angeles, and Attending Staff, St John's Hospital, Santa Monica, and Alhambra Community Hospital, Alhambra, California. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1987. 94 pages, $30 (paperback).